Clinics of Surgery

Research Article ISSN: 2638-1451 | Volume 7

Prognostic Significance of Platelet to Lymphocyte Ratio in Gallbladder Cancer: A Meta-Analysis

Wei L, Xie N, Cao F, Li CM and Fu BM

Departments of 1Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, P.R. China

***Corresponding author:**

Bi-Mang Fu,
Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital of Kunming Medical University, 374 Dianmian Main Road, Kunming 650101, Yunnan, P.R. China.
Tel: +86 871 63402881; Fax: +86 871 63402880;
E-mail: fubimang@163.com

Keywords:

Gallbladder cancer; platelet; lymphocyte

Received: 02 Feb 2022
Accepted: 15 Feb 2022
Published: 21 Feb 2022
J Short Name: COS

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Citation:

Fu BM, Prognostic Significance of Platelet to Lymphocyte Ratio in Gallbladder Cancer: A Meta-Analysis. Clin Surg. V7(4): 1-6

1. Abstract

1.1. Objective: To investigate the effectiveness of the prognostic roles of PLR in GC patients by performing meta-analysis.

1.2. Methods: We carried out a systematic literature search in three databases (PubMed, Embase, and Web of Science). Pooled Hazard Ratios (HR) and 95% confidence intervals (95% CI) in the including studies were extracted.

1.3. Results: We summarized the available evidence from 8 studies with a total of 1526 cases. The pooled results indicated that high PLR is a significant predictor of poor OS (HR =1.48, 95%CI: 1.19-1.83). Subgroup analysis based on stage demonstrated PLR is not significantly associated with advanced GC, PLR>140, and more than 200 patients in the study.

1.4. Conclusion: In conclusion, the present study demonstrates that preoperative PLR is a prognostic marker in GC.

2. Introduction

The inclusion criteria for each study were as follows: (1) GC was diagnosed by pathological or radiological results; (2) platelet and lymphocyte was measured by hematology test results before treatment; (3) hazard ratios (HR) and 95% confidence intervals (95%CI) for PLR were described in the study or provided enough information to calculate. Literatures were excluded in the current study: (1) animal studies, reviews, abstracts, letters, case reports and meetings reports, full text not available; (2) duplicate articles; (3) no HR value provided and /or cannot be calculated (Table 1).

Table 1: Characteristics of the included studies

Author/ year	Country	Treatment	Sample size	TNM stage	Mean/ median ages (years)	Follow-up time (months)	Cut-off value	Outcome	NOS score
Zhu 2019	China	surgery/ conservative treatment	255	all	63	60	143.77	OS	8
Deng 2019	China	surgery	169	all	64	NA	145.33	OS	9
Choi 2019	Korea	Chemotherapy	178	III/IV	64	NA	108	OS	9
Du/2018	China	NA	220	III/IV	NA	36	178	OS	8
Tao 2018	China	Surgery/ Chemotherapy	84	III/IV	62	NA	117.75	OS	9

Cui 2018	China	Chemotherapy/ radiotherapy/ intervention surgery/ palliative care	159	all	64	36	181.85	OS	9
Zhang 2015	China	surgery	145	all	NA	60	113.34	OS	8
Pang 2015	China	surgery	316	All	65	60	117.7	OS	8

3. Data Extraction

The main characteristics from each included study were extracted independently by two investigators and disagreement was resolved by joint discussion. Extracted the following data: first author, publication year, country, sample size, age of patients, cut-off value [1-5] of preoperative PLR, HR value and 95% CI, treatment methods, time of follow-up, TNM stage. The research quality of each included study was assessed using the 9-star Newcastle-Ottawa Scale (NOS) by two independent reviewers (Lei Wei, Chun-Man Li). NOS scores of greater than or equal to 6 were regarded as high-quality studies (Table 2).

Table 2: Characteristics of the included studies

Covariates	Subgroup	No. of studies	Number of patients	HR (95% CI)		Heterogeneity		Meta-regression P
				Random-effects model	Fixed-effects model	P	I^2	
Overall		8	1526	1.48(1.19,1.83)		0.023	56.90%	
Therapies	Surgical resection	3	630	1.73(1.41,2.12)	1.73(1.42,2.11)	0.351	4.60%	0.287
	others	5	896	1.31(0.96,1.79)	1.33(1.10,1.59)	0.034	61.70%	
stage	III/IV	3	567	1.34(0.69,2.59)	1.46(1.09,1.95)	0.008	79.50%	0.756
	All stage	5	959	1.51(1.24,1.84)	1.51(1.30,1.76)	0.171	37.50%	
Cut-off value of PLR	>140	4	803	1.26(0.84,1.89)	1.34(1.11,1.62)	0.005	76.40%	0.295
	<140	4	723	1.68(1.39,2.03)	1.68(1.39,2.03)	0.819	0	
Number of patients	>200	3	791	1.17(0.75,1.83)	1.34(1.10,1.63)	0.016	76%	0.217
	<200	5	735	1.66(1.34,2.07)	1.66(1.38,1.99)	0.241	27.10%	

4. Data Analysis

HR and their associated Standard Errors (SE) were pooled to give the effective value for the quantitative aggregation of the survival results. Meta-analysis was conducted using STATA software (version 12.0). Statistical heterogeneity was assessed by the chi-squared and I-squared tests. if I2≥ 50% or/and P < 0.10, random-effect model was used to calculate the pooled HR and 95% CI [6-10]. Otherwise, a fixed-effect model was used. Visual inspection of the funnel plot was used to determine potential publication bias, P <0.05 indicates statistically significant publication bias. All statistical tests were two-sided, and statistical significance was defined as P<0.05.

5. Results

5.1. Characteristics of Included Studies

The flow chart of the process of literature retrieval and screening is shown in Fig. 1. A total of 8 studies 15-22 published between 2015 and 2019 were identified and all these trials were retrospective cohort studies with 1526 patients enrolled in this meta-analysis [11]. The basic characteristics of the included studies were summarized and presented in Table 1. Seven studies were conducted in China; one study was conducted in Korea. 630 patients with GC received surgical treatment alone; other patients received surgery combined with chemotherapy, chemotherapy, radiotherapy or palliative care. The PLR cut-off values in these studies were determined by different methods and ranged from 108 to 181.85 [12-14].

5.2. Quality Assessment

As Table 1 show, there are four studies with a NOS score of 9, four studies with a NOS score of 8 according to the NOS criteria. All of the studies possessed good quality according to our definition for high-quality studies (Figure 1).

5.3. Effect of Preoperative PLR On OS for Patients with GC

All of the studies reported the prognostic value of PLR for OS [15]. A random-effects model was used to pool all the included studies and demonstrated a high preoperative PLR was associated with a poor OS with a HR value of 1.48 (95% CI: 1.19–1.83) with inter-study heterogeneity (I2 = 56.9%, P = 0.023) (Figure 2).

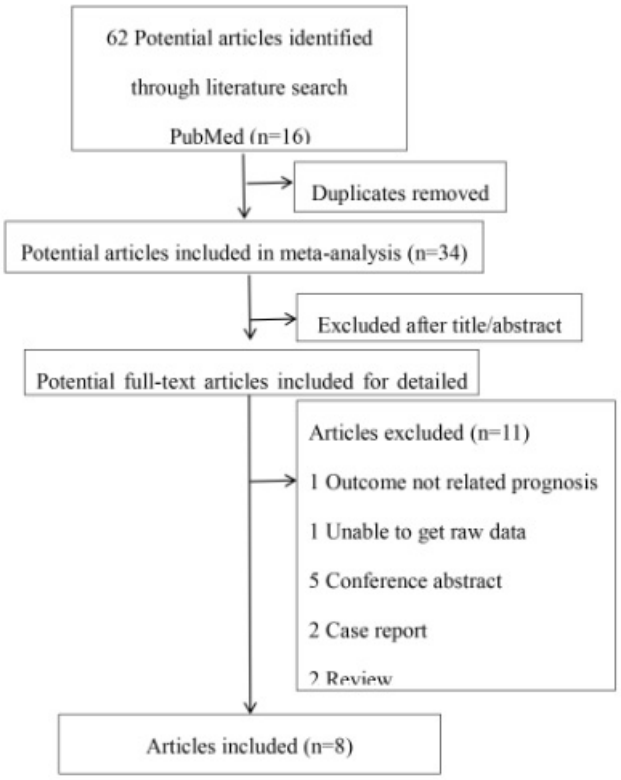


Figure 1: Flow chart of literature search and study selection

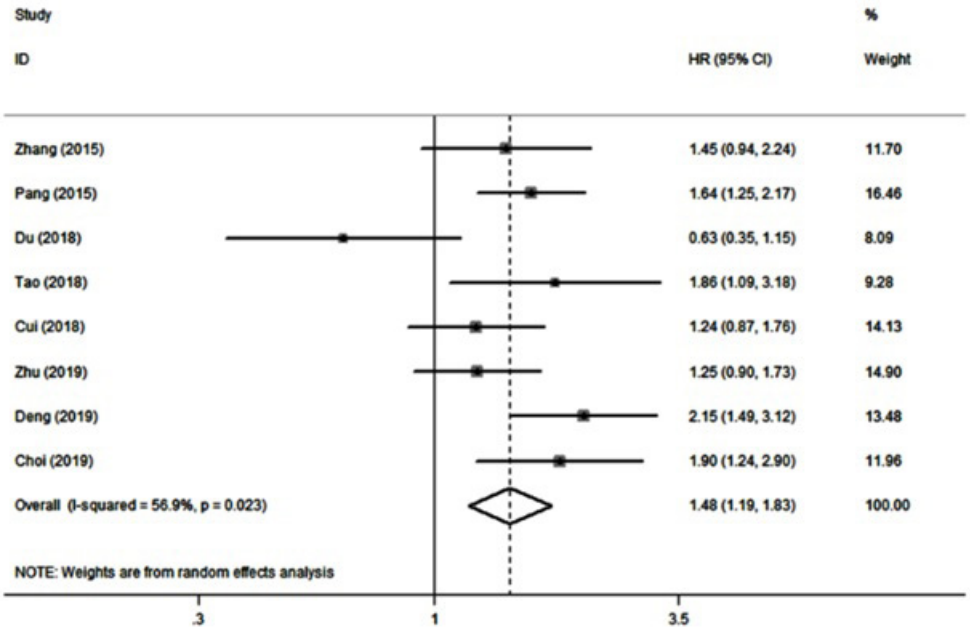


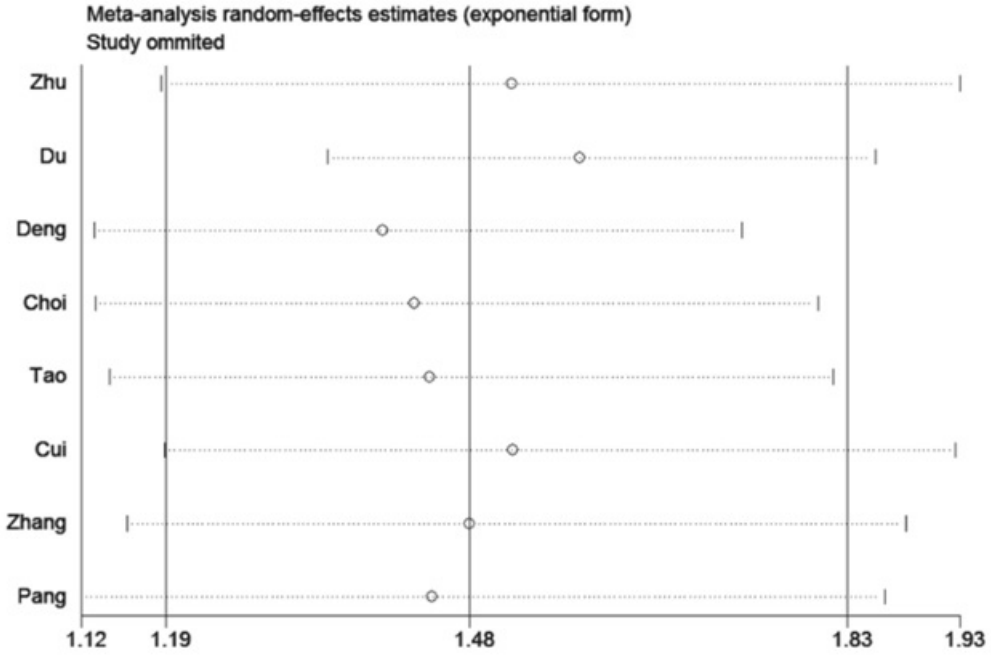
Figure 2: Forest plots depicting OS reported in the included studies. HR is shown with 95% CI. CI: confidence interval

5.4. Subgroup Analysis

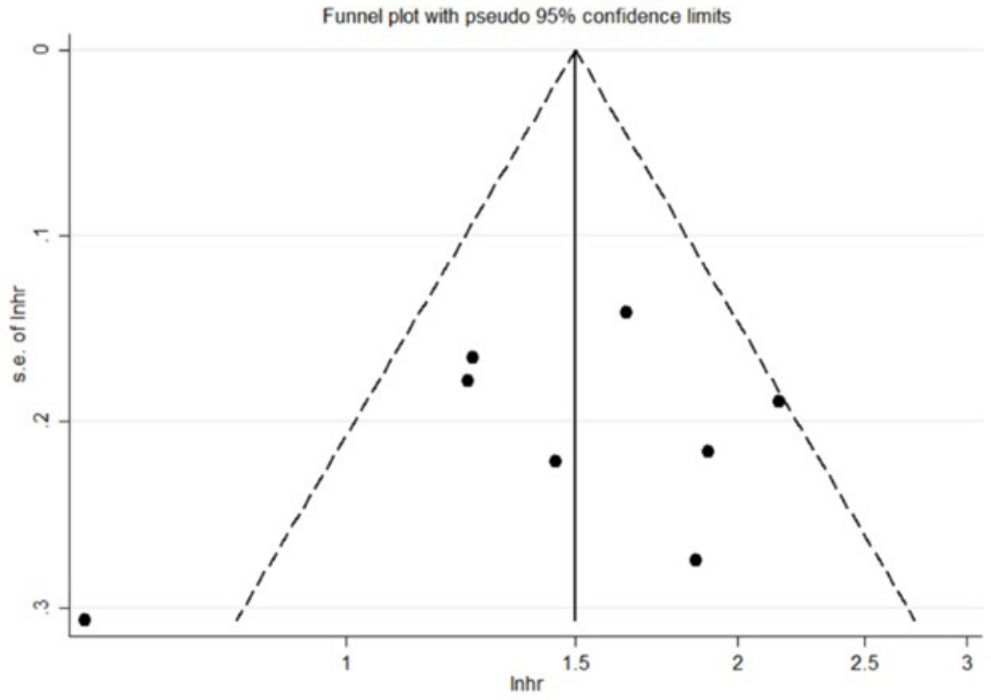
Due to the high I2 and P values in the pooled analysis, subgroup analyses were also performed. We analyzed several possible sources of heterogeneity summarized the results in (Table 2). After the introduction of the regression model with the four factors, there was no potential source of heterogeneity found following meta-regression. Interestingly [16, 17, 20] PLR has little value in the stage subgroup of III/IV, cut-off value of PLR subgroup with >140, and number of patient's subgroup with more than 200 patients. Marginally statistical non-significance was found in not treated with surgery alone.

5.5. Sensitivity Analysis and Publication Bias

Influence analysis was performed and demonstrated that no one study could overly affect the summary of OS risk estimate (Supplementary Figure 1). Publication bias was assessed by funnel plot analysis and the plots showed basic symmetry (Supplementary Figure 2). No significant publication bias was further determined by Begg's test, with a P value of 0.902 [18, 19].



Supplementary Figure 1: Influence analysis for the studies



Supplementary Figure 2: Funnel plot of comparison of the included trials

6. Discussion

A large number of studies have studied the prognostic value of pretreatment PLR in GC, but there is no consistent and clear conclusion yet. Therefore, we reviewed the available studies and performed a meta-analysis to evaluate the prognostic value of PLR in GC [21, 22]. Our meta-analysis included 8 articles, including 1526 patients with GC, showed that higher PLR is related to shorter OS (HR: 1.48 95% CI: 1.19–1.83) of GC patients. However, in the subgroup analysis, PLR seems to have no prognostic value in some subgroups, which may require more research and more detailed grouping in the original study.

Previously, a meta-analysis demonstrated that high PLR is associated with poor prognosis in different BCLC stages HCC patients and PLR could be used as a marker to predict the survival rate in HCC patients [23]. In a meta-analysis on the relationship between biliary tract cancer which included 2 studied about GC and PLR, showed that high PLR predicted decreased OS in patient with biliary tract cancer, and subgroup analyses also showed the same results [24]. Moreover, in a conference abstract, NLR, PLR and Monocyte-To-Lymphocyte Ratio (MLR) are promising biomark-

ers for worse survival in GC [25].

High PLR always indicate the increase of platelet count, decrease of lymphocytes, or all of the both. The mechanisms of high PLR related to poor cancer prognosis is still unclear, maybe due to the following reasons: firstly, increased platelets can secrete cytokines and promote the growth of tumor cells [26], platelet can promote the invasion and recurrence of tumor cell, it is one of the sources of VEGF and transforming growth factor β (TGF-β) which can affect tumor formation [27]; secondly, lymphocytes play the role of immune surveillance and immunoediting, which can affect the residual and micrometastasis of tumor cells, and then affect the proliferation and metastasis of tumors [28], the tumor patients with increase of lymphocytes can have better treatment response [29], lymphocytopenia is also related to tumor burden and distant metastasis [30].

Although our research implemented strict following of the protocol and inclusion criteria, there are still some limitations. There is obvious heterogeneity in our meta-analysis. Firstly, although sensitivity analysis and meta-regression are used, the source of heterogeneity cannot be found Secondly, the studies we have included are all from Asia, and the conclusions reached may be geographically restricted Thirdly, all the included literature is a retrospective study Fourthly, there is publication bias in our current study. The underlying reason may be that the published articles are more biased towards positive results; Fifthly, at present, the cut off value of PLR is not unified, and different values may lead to different conclusions; Finally, Begg's test has a relatively low test power, when the number of documents analyzed is less than 10.

In conclusion, we could cautiously come to the conclusion that elevated preoperative PLR are associated with poor prognosis in GC patients, and they should be used as markers to predict the survival rate and assess the outcomes in GC patients.

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